COVID-19 Global Consultation on Correlates of Protection

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Overview of Human Challenge Studies – COVID-19

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Volunteer challenge studies are a powerful and useful tool

Information challenges can provide

- Establish pathogenicity
- Elucidate pathogenesis
- Identify host risk factors
- **Estimate infective inoculum**
- **Assess infection-derived immunity**
- **Characterize the immune response**
- **Preliminary measurement of vaccine efficacy**
- **Identify correlates of protection**
- Assessment of new therapeutic agents

Is the pathogen amenable to a model?

- Clinical severity of natural disease?
- Is the illness treatable?
- Is the illness reliably self-limited?
- Risk to the community?
- Is physical containment required?
- Quarantine (compulsory isolation) required?
- Document subject's baseline health?
- Can subjects' follow-up be assured?

Human Challenge Studies to Accelerate Corona Virus Licensure.

Nir Eyal, Marc Lipsitch, Peter G Smith.

Journal of Infectious Diseases 2020; 221:1751-1756

"By replacing conventional phase 3 testing of vaccine candidates, such trials may subtract many months from the licensure process, making efficacious vaccines available more quickly."

Why Challenge Trials of SARS-CoV-2 Vaccines Could Be Ethical Despite Risk of Severe Adverse Events

Nir Eyal.

Ethics & Human Research 2020; 42:24-34.

Extraordinary Diseases Require Extraordinary Solutions.

Stanley A Plotkin & Arthur Caplan.

Vaccine 2020; 38: 3987-3988

So much at stake: Ethical tradeoffs in accelerating SARS-CoV-2 vaccine development

Christine Grady, Seema Shah, Franklin Miller,et al.

Vaccine 2020; 38:6381-6387

For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development

Jeffrey P Kahn, Leslie Melttzer Henry, Anna C Mastroianni, Wilbur H Chen, Ruth Macklin

Proc Nat'l Acad Sci, USA 2020; 117:28538-28542

Human Challenge Studies with Wild Type SARS-CoV-2 Violate Longstanding Codes of Human Subjects Research

Stanley M Spinola, et al.

Open Forum Infectious Diseases 2020

Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Viewpoint of a WHO Advisory Group Tasked to Consider Establishing a Closely-monitored Challenge Model of Coronavirus Disease 2019 (COVID-19) in Healthy Volunteers

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Several factors warrant special caution with SARS-Cov-2

- **High transmissibility of SARS-CoV-2 from person-to-person**
- **Severity of COVID-19 in certain sub-populations** (elderly, diabetics, hosts with pulmonary and cardiac disease). Thus, need for a high containment facility and compulsory isolation to prevent inadvertent transmission to a high-risk bystander contact
- Occasional extended (“long COVID”) disease **in young adults**
- Debate on reliability of “rescue treatment” to arrest the progression of COVID-19 illness from a mild/moderate illness to serious, potentially life-threatening illness.

Advisory Group Recommendations - June 2020

1) **Incremental STAGE 1 / STAGE 2 strategy**
2) Restrict to healthy individuals **18-25 years of age**
3) **Perform STAGE 1 in High-Level Isolation Units**
4) **Legal Quarantine (Compulsory Isolation)**
5) **Selecting isolates for BSL-3 GMP manufacture**
6) GMP manufacturer: **frozen liquid formulation in vials**
7) **$1x10^2$ $TCID_{50}$, $1x10^3$ $TCID_{50}$, $1x10^4$ $TCID_{50}$**; maybe **$1x10^5$**
8) Follow progress of treatment trials globally to identify a credible “rescue treatment”

Research groups that have established COVID-19 volunteer challenge models or have taken some steps to prepare for human challenges

Country	Group	Gov't Approval to begin	Protocol	Ethics Comm Approval	GMP Lot of virus	Type of virus	High Level Isolation Facility	Com-pulsory contain-ment	Start Date
UK*	Imp Coll, Oxford, hiVivo	Yes	Yes	Yes	Yes	D614G	Yes	No	Q2 2021
Nether-lands*	Univ. of Leiden	No (wait & see)	Yes	No	No	TBD	?	No	On hold
Belgium	U of Antwerp	In general	Not yet	Not yet	No	-	Being built	No	2022
USA	NIH	No	Yes	No	Yes	D614G	Yes	Maybe	No plans to begin

* These models primarily aim to study nasopharyngeal shedding of SARS-COV-2 but not to study illness.

MML Question 1. Can you provide a brief update of your model development and use?
Helen McShane: We are still in the dose escalation phase infecting previously infected subjects. Have inoculated 8 with 10^1 $TCID_{50}$ and are now evaluating 10^2 $TCID_{50}$
Christopher Chiu: The seronegative dose-finding study with the pre-alpha virus has completed the quarantine phase and settled on a dose of 10^1 $TCID_{50}$.

MML Question 2. Have you done virus challenge of volunteers vaccinated with a vaccine for which there are field trial efficacy data?
HMcS: None of our volunteers have been vaccinated. We have now removed this as an exclusion criteria as most people in the UK have now been vaccinated. So, our new criteria are must have had past infection and can have been vaccinated (but not compulsory).

MML Question 3. Have you done any challenges with either VoC Delta or Gamma?
HMcS: To date we have only used the Wuhan strain. Plans underway to manufacture a delta strain to GMP for use in the model.
CC: Manufacturing of a new VOC strain (likely delta) is underway. A study to characterize this strain in the model will take place once the challenge agent is ready. The main sources of delay are obtaining suitable clinical isolates, since these need to have low Ct values to grow up successfully, and unpredicted delays due to growth failure and contamination.

MML Question 4. Does your model involve just virus shedding, or is there a mild clinical component that can be scored in looking for a correlate of protection if there was challenge of vaccinated volunteers (or re-challenged volunteers, or persons who recovered from known VoC illness)?
HMcS: We monitor symptoms when subjects are infected, but use pre-emptive therapy should these become anything more than mild so limited clinical data only.
CC: In seronegative volunteers, most infected volunteers are mildly symptomatic with a few asymptomatic. So it will be possible to correlate immune factors with differences in symptom severity. Of course, this may differ in those with partial previous immunity.

MML Question 5. What is the maximum number of volunteers that can be challenged at one time in your high containment facility?
HMcS: Five. We also have another 10 beds in Oxford potentially available from the end of the year.
CC: There are currently 19 suitable beds in London. We are working on increasing capacity in London at other sites, which hopefully will come on-line later this year.

MML Question 6. Is there other information that you and your colleagues have that relates to the Delta VoC and correlates of protection against infection or against clinical illness caused by Delta (or another variant of SARS-CoV-2) that you believe can be helpful to WHO in its quest.
HMcS: We are comprehensively interrogating the baseline immune response in our subjects who are previously infected to identify the potential COP.

Considerations of whether/when to initiate COVID-19 challenges

1) Try to coordinate the timing of COVID-19 challenge models with broader regional and international COVID-19 control priorities.

2) Challenge studies should prioritize **answering questions that cannot be answered in other ways.**

3) Human challenges have not yet proven to be nimble. **Takes 4-6 months to make up GMP lots**

4) Additional COVID-19 vaccines are needed and there are many candidates. Could challenge studies play a constructive role?

- **Yes, for new vaccines delivered by the intranasal route**

9) COVID-19 human challenges and public perception

-- Country and context-specific
-- Vaccine hesitancy
-- Conspiracy theories and social media disinformation of anti-vaccine groups

Summary comments on challenge models relevant to correlates of protection

1) Preliminary COVID-19 challenge models have been established (in seropositives and in seronegatives)

2) Investigators have closely followed WHO AG guidelines (except for Compulsory Containment)

3) These first models are mainly infection (virus shedding) models

4) A very low (10^1 $TCID_{50}$) dose infects volunteers.

5) The first model utilized an early SARS-CoV-2 strain

6) The early human COVID-19 challenge is not yet nimble vis a vis emerging Variants of Concern.
Currently takes 4-6 months to make up a new GMP lot.
Must perform a dose response study with the new virus lot.

Can this model contribute to understanding Correlates of Protection?

-- Potentially, could be very useful for studying CoP against nasal shedding of wild virus

-- May be very useful for studying the efficacy of intranasal COVID-19 vaccines in preventing SARS-CoV-2 shedding from the upper respiratory tract and in preventing mild upper respiratory clinical illness.

-- May be useful for studying the impact on virus shedding in volunteers who have received passively-administered parenteral hyper-immune globulin

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